IGF2BP3 inhibition: another home run for RNA-binding protein targeting in hematological malignancies

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RNA-binding proteins (RBP) are critical regulators of gene expression, affecting RNA processing till translation. More than 1,500 proteins have been catalogued as RBP in the human genome.[1] RBP are very diverse in respect to structure, characteristic of the RNA-binding domain and function. In fact, RBP are notoriously multifunctional with some of them showing great target diversity and ability to bind both messenger RNA (mRNA) and different types of non-coding RNA. By orchestrating the expression of gene networks, RBP modulate complex biological processes such as differentiation and cell-fate decisions.[2] In cancer, aberrant expression of RBP has been reported over the years in multiple solid tumors and hematologic malignancies. Their subsequent molecular characterization and genomic analysis led to the identification of "oncogenic" RBP and provided maps of their target genes. Despite their relevance and established role in tumorigenesis, RBP have not been fully explored as candidate targets in cancer therapy. Targeting these proteins offers a powerful strategy to simultaneously modulate multiple oncogenic pathways due to their broad regulatory impact on numerous transcripts.[3,4] Barriers to select candidates, such as characteristics of RNA-binding motifs, essential regulatory roles in normal cells and patterns of expression, have discouraged systematic investigation of RBP as therapeutic targets. The brave work of several research groups kept the field alive. Many identified RBP inhibitors showed excellent potential in preclinical and clinical studies. Some protein families, including Musashi, heterogeneous RNP and ELAV, received special attention. In hematologic malignancies, two success stories should be highlighted. Splicing factor 3B subunit 1 (SF3B1) is the most recurrently mutated gene in myelodysplastic syndrome and chronic lymphocytic leukemia. Mutant SF3B1 creates a cancer dependency, accelerates the onset and increases leukemogenesis. Several SF3B1 inhibitors have been developed and are currently being evaluated in clinical trials.[5] Nucleophosmin 1 (NPM1) is a multi-function RBP, being particularly relevant in ribosome biogenesis. NPM1 mutations occur in more than 30% of cases of *de novo* acute myeloid leukemia and promote re-localization of the protein to the nucleus. Mutant NPM1 interacts with the menin-KMT2A complex, activating stem-cell programs. An inhibitor of this interaction induced complete remissions in acute myeloid leukemia with an NPM1 mutation, and the drug was recently approved by the Food and Drug Administration for therapeutic use.[6]

The insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family, which includes IGF2BP1, IGF2BP2, and IGF2BP3, checks all the boxes as an ideal therapeutic target. These oncofetal proteins are highly expressed during embryogenesis but barely detectable in most adult tissues. IGF2BP expression gets re-activated in tumors and high levels of expression of these RBP have been detected in

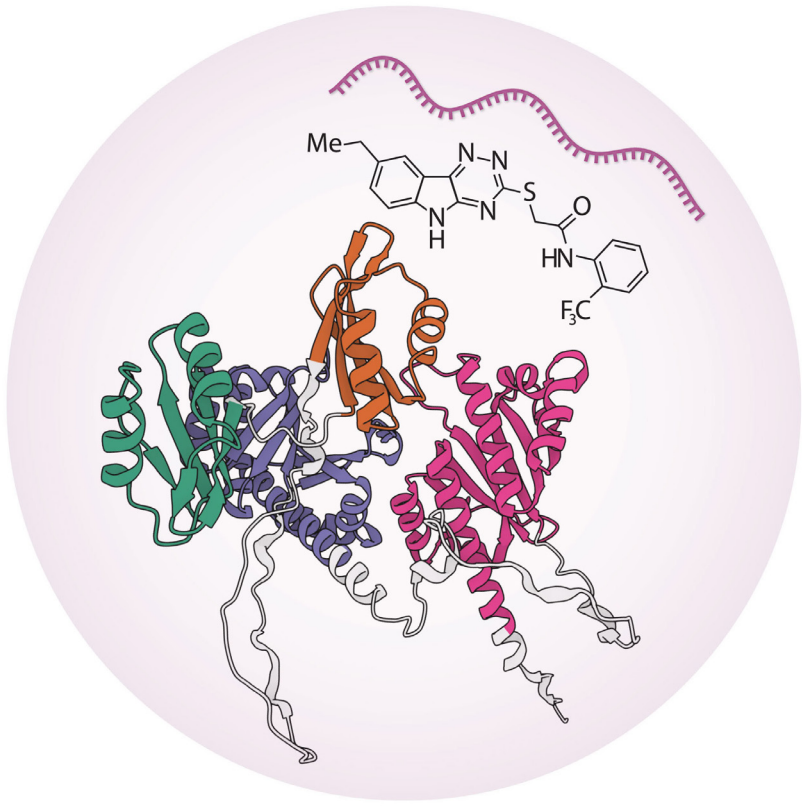

Figure 1. I3IN-002 disrupts the interaction between the oncogenic RNA-binding protein IGF2BP3 and its RNA targets.

diverse cancers. They stabilize and enhance the translation of potent oncogenes such as *MYC, CDK6*, and *HOX9*. Their regulatory roles, mechanisms of action and binding motifs are well characterized, providing additional information to develop strategies for the identification of inhibitors.[7]

IGF2BP3 is upregulated in *MLL*-translocated B-cell acute lymphoblastic leukemia. Previous work from Rao's laboratory established that deletion of IGF2BP3 delays leukemia development and extends leukemia-free survival.[8,9] In this issue of *Haematologica*, Jaiswal *et al.*[10] report their findings on a novel IGF2BP3 inhibitor that showed excellent results in preclinical studies. The authors used a strategic screening platform that took advantage of IGF2BP3's unique RNA-binding motif, which includes an m6A modification. A common tactic employed in RBP inhibition is to disrupt the RBP-RNA interaction by using competing molecules. Jaiswal *et al.* screened close to 200,000 compounds in a time-resolved fluorescence energy transfer (TR-FRET) assay that used a green fluorescent protein-tagged IGF2BP3 protein and a biotinylated RNA oligo with a target sequence. The top hit compound, I3IN-002, showed excellent results *in vitro,* in particular against B-cell acute lymphoblastic leukemia cell lines with the *MLL-AF4* translocation. *In vivo*, treatment expanded leukemia-free survival. I3IN-002 was not the first identified IGF2BP3 inhibitor but it was the first to be tested against hematologic malignancies and the first proven to efficiently disrupt IGF2BP3's binding to its target RNA and affect their expression. A key finding was the significant enrichment of compounds with an indolyltriazine group among the top hits in the screening. These results suggest that indolyltriazine groups might favor RNA-protein binding, a hypothesis meriting further structural investigation. These results could provide important information and fast-track the development of inhibitors against other oncogenic RBP.

While I3IN-002 is not yet ready to move to the clinic, the results are very promising. With focused medicinal chemistry optimization, we will soon see an IGF2BP3 inhibitor ready for therapeutic use. Overall, the results of Jaiswal and colleagues serve as motivation for the scientific community to keep exploring RBP targeting as alternative therapeutic routes.

Disclosures

No conflicts of interest to disclose.

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